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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,935	08/09/2006	Mladen Mercep	PLP528USW	9193

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
07/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,935	MERCEP ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/15/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 12, and 15 have been amended and Claims 10 and 11 have been cancelled by the Applicant in correspondence filed on 05/18/2009. Claims 1-9 and 12-15 are currently pending. This is the second Office Action on the merits of the claim(s).

Specification

2. Examiner acknowledges Applicants' amendment to page 15 of the instant specification. Examiner agrees that no new matter has been added.

RESPONSE TO ARGUMENTS

3. Claim 15 was objected to because "chloro" was misspelled. This objection is moot in light of the amendment to Claim 15.

4. Claims 1-15 were rejected under 35 U.S.C. 112, first paragraph, for failing to be enabled for a method of treating using a solvate of formula (I). The amendment to Claim 1 does not overcome this rejection because Applicants state that "a compound of formula (I)" necessarily encompasses solvates of said compound in reply filed on 05/18/2009 (pg 1, para 4, lines 3-6). Therefore, the rejection of Claims 1-15 under 35 U.S.C. 112, first paragraph, for failing to be enabled for a method of treating using a solvate of formula (I) is maintained.

5. Claims 1-15 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administrating a compound of formula (I), or salt thereof,

for the treatment of depression, bipolar disorders, addiction, anorexia, stroke, Alzheimer's disease, and Parkinson's disease, does not reasonably provide enablement for administrating a compound of formula (I), or salt thereof) for the treatment of any CNS-related disease, damage, or disorder not listed above, or prevention of any CNS-related disease, damage, or disorder (including those listed above). This rejection is moot in light of the amendment to Claim 1 and the cancellation of Claims 10 and 11.

6. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercep, et al. (International Application No. WO 01/087890, provided in IDS) in view of King (Medicinal Chemistry, 1994, provided in IDS), Müller and Ackenheil (Progress in Neuropsychopharmacology and Biological Psychiatry, 1998), and Tobinick (US Patent No. 6,471,961, 2002). This rejection is moot in light of the amendment to Claim 1 and the cancellation of Claims 10 and 11.

7. Claims 1-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Andrés-Gil, et al. (International Application No. WO 99/19317, provided in IDS). Claim 15 was rejected under 35 U.S.C. 103(a) as being unpatentable over Andrés-Gil, et al. (above) as applied to claims 1-14 above, and further in view of King (above). Applicants traversed this rejection on the grounds that the compounds disclosed by Andrés-Gil, et al., are not obvious variants of the instantly disclosed compounds. Specifically, the 5-membered ring of Andrés-Gil, et al., is fully saturated whereas the 5-membered ring of the instant application is unsaturated. After careful consideration, Examiner finds Applicants' arguments persuasive and the rejections of Claims 1-14 over Andrés-Gil, et al., and Claim 15 further in view of King are withdrawn.

8. Amended Claims 1-9 and 12-15 are examined on their merits and the following **FINAL** rejection is made.

Claim Rejections - 35 USC § 103

9. The text of Title 35, U.S.C. § 103 can be found in a prior Office action.

10. Claims 1-9 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercep, et al. (above), in view of Tobinick (US PreGrant Publication no. 2003/0049256) and King (above).

11. Amended Claim 1 of the instant application is drawn to a method of depression, bipolar disorder, addiction, and/or stroke associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administration of a compound of formula (I). Claim 2 limits the biogenic amine to serotonin, norepinephrine, or dopamine. Claim 3 limits the neurotransmitter to glutamate. Claims 4-9 limit the intended result of the compounds (i.e. binds to the receptor of a biogenic amine). Claims 12-15 limit the substituents of the compound of formula (I). The elected species [3-(11-chloro-1,8-dioxa-dibenzo[e,h]azulen-2-ylmethoxy)-propyl]dimethyl-amine reads on all of the claims, and is specifically listed in Claim 15.

12. Mercep, et al., teach the compound [3-(11-chloro-8-oxa-1-thia-dibenzo[e,h]azulen-2-ylmethoxy)-propyl]dimethyl-amine (Example 11) as an inhibitor of TNF-α and IL-1. The compound taught by Mercep, et al., differs from the elected species only in that the furan of the elected species is replaced by a thiophene in the prior art. King teaches that -S- and -O- are bioisosteres (Table 1), such that one of ordinary skill in the art would reasonably expect that the two compounds would behave in a similar fashion (e.g. the elected species would be an inhibitor

of TNF-α and IL-1, like the compound taught by Mercep, et al.), absent evidence to the contrary. Mercep, et al., and King do not teach the elected species for the treatment of depression, bipolar disorder, addiction, and/or stroke.

13. Applicants' argument that King is not applicable to the instant claims is not persuasive. Applicants assert that King provides no motivation to one of ordinary skill in the art to substitute -S- of Mercep, et al., with -O- to arrive at the instantly claimed compound. Applicants contend that King cites the "unpredictable effects upon biological activity" of substituting -S- for -O-. Moreover, Applicants question why an art worker would substitute only -S- for -O- when King discloses numerous bioisosteres. Examiner respectfully disagrees with Applicants' interpretation of King.

14. King discloses potential pitfalls for a skilled artisan to be conscious of when creating bioisosteres of a given molecule. However, given the similarity of oxygen and sulfur, one of ordinary skill in the art would reasonably expect that oxygen can be substituted for sulfur with little biological effect on the resultant molecule. Indeed, it would be unexpected for the resultant molecule (that of the instant application) to not behave in a similar manner as the parent molecule (that disclosed by Mercep, et al.). Furthermore, as decided in *Ex parte Engelhardt,* 351, 208 USPQ 343 (Bd. Pat. App. & Int., 1980), and affirmed in *In re Merck,* 231 USPQ 375 (Fed. Cir., 1986), "isosterism does not permit a medicinal chemist to predict the potential properties of a new isosterically related compound with absolute certainty, it does provide suggestion of areas of biological activity. In any event, absolute predictability is not required by the Patent Statues. Section 103 of the Statues merely requires that there be a 'reasonable expectation, or some predictability.'"

15. That the King teaches many isosteres and Examiner selected one substitution among many possible substitutions and that King fails to teach which location of the compounds by Mercep, et al., may be substituted is not persuasive. Given the structure of Mercep, et al., limited substitution form that of King are possible, that ring replacements are the easiest, most predictable, and most commonly done in isosteric replacements, and because King teaches limited ring equivalents in table 1 and specifically cites furan and thiophene as examples of ring equivalents, one would have been motivated to start by replacing thiophene with furan or vice versa. "[O]ne of ordinary skill in medicinal chemistry would have looked to the concept of bioisosterism as a routine tool in his/her research" of drug development. *Ex parte Engelhardt,* 208 USPQ 343, 351 (Bd. Pat. App. & Int., 1980). Applicant also argues that King fails to teach or suggest the instant substitution of Mercep, et al., compounds. The recent decision in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct 1727, 82 USPQ2d 1385, 1394, 1396 (2007), foreclosed this argument. Also, Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is from general knowledge of bioisosteres equivalent of furan and thiophene rings, which has been available to one of ordinary skill in the art for several years prior to the date of this invention. Per MPEP § 2144.06, if equivalency is recognized in the prior art, it is obvious to substitute one for the other. Thus, one of ordinary skill in the art would

reasonably expect the compounds of Mercep, et al., and those of the instant application would have the same utility (inhibitor of TNF-α and IL-1), absent evidence to the contrary.

16. Tobinick teaches that molecules that block the action of TNF-α and IL-1 are useful for the treatment of depression, bipolar disorder, addiction, and stroke (abstract; para 0002 lines 4-10, 35-37; para 0003, lines 10-15). Since depression, bipolar disorder, addiction, and/or stroke comprise an inflammatory component mediated by TNF-α and IL-1, it would have been *prima facie* obvious to use known TNF-α and IL-1 inhibitors for the treatment of these diseases.

17. Claims 4-9 contain wherein clauses indicating the intended result of the method of treatment (e.g. binding to the receptor of a biogenic amine). Such an intended result is not considered to be a patently distinguishing feature as any compound that reads on Claim 1 would also have the intended result of Claims 4-9. A "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005).

18. Applicants' contention that they have discovered a novel mechanism by which the claimed compounds exert their therapeutic effect is not considered a patentably distinguishing feature of the invention. '"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.' *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." (MPEP § 2112(I)) One of ordinary skill in the art would have been motivated to use the compounds of

formula (I) for the treatment of depression, bipolar disorder, addiction, and/or stroke based on the reasonable expectation that these compounds also inhibit TNF-α and/or IL-1.

Conclusion

19. Claims 1-9 and 12-15 remain rejected.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/San-ming Hui/
Primary Examiner, Art Unit 1617